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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,450	GORR ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 16 May 2008 has been entered.

2. Claims 1-3 and 17 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

4. Claims 1-3 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reutter et al (1996, Plant Tiss. Cult. Biotechnol. 2:142-147) in view of Lee et al (US Patent 6,020,169, filed April 1998). The rejection is repeated for the reasons of record as set forth in the Office action mailed 24 September 2007. Applicant's arguments filed 16 May 2008 have been fully considered but they are not persuasive.

The claims are drawn to a method of isolating a heterologous protein from culture medium in which in transformed *P. patens* protonema were grown.

Reutter et al teach growth of *P. patens* protonema transformed with a nucleic acid encoding a heterologous protein in a bioreactor culture (pg 143, paragraph 2-3) and that these protonema produced large amounts of the heterologous protein grown in bioreactor culture (pg 143, paragraph 3; Fig. 2-3; claim 1). Reutter et al also teach that *P. patens* can be grown on

inorganic medium (pg 142, paragraph 4). Reutter et al do not disclose isolation of the protein from the culture medium.

Lee et al teach isolation of biologically active heterologous protein from tobacco cells grown in suspension culture. The cells were transformed with a nucleic acid encoding Mab HC operably linked to a mammalian secretion signal peptide (column 12, line 5, to column 19, line 67). The Mab HC was selectively secreted into the medium (column 16, lines 14-45).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of producing heterologous protein in *P. patens* protonema as taught by Reutter et al, to use a signal peptide in the transformation construct and isolate the protein from media as described in Lee et al. One of ordinary skill in the art would have been motivated to do so because of the advantages of being able to isolate the protein from the medium (Lee et al, column 4, lines 34-54).

Applicant urges that Reutter described the cultivation of moss protonema and production of heterologous proteins inside that tissue; the combined disclosures only relate to the destruction of the producing tissue of intact plants (response pg 7).

This is not found persuasive because Lee shows that heterologous protein could be collected from the medium. The combined disclosures would obviate the need to destroy producing tissue of intact plants.

Applicant urges that this shows that those of skill in the art cannot obtain any motivation leading to the solution of the present invention; with Lee and Raskin the heterologous protein even with a signal sequence travels only to the apoplastic space (response pg 7-8).

This is not found persuasive because Lee shows that this is sufficient to get protein into the medium.

Applicant urges that none of the references teach or suggest obtaining secreted heterologous proteins from intact protonema; further one of ordinary skill in the art would not have a reasonable expectation of success (response pg 8).

This is not found persuasive because the rejection is based on a combination of references. As discussed below, Applicant has not shown that one of ordinary skill in the art would not have a reasonable expectation of success.

Applicant urges that Reutter is silent with respect to obtaining the heterologous protein without disrupting the tissues or cells (response pg 9).

This is not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection is based on a combination of references, and is not a 102 rejection.

Further, *KSR* makes it clear that a teaching, suggestion or motivation does not need to be explicitly provided by the prior art references.

Applicant urges that the Reski Declaration of record indicates that in Reutter the protein was localized in cells and no secretion was observed; thus, Reutter neither teaches nor suggests there would be secretion through the wall (response pg 9).

This is not found persuasive because the rejection is based on a combination of references. *KSR* makes it clear that a teaching, suggestion or motivation does not need to be explicitly provided by the prior art references.

Applicant urges that it is known that single-cell cultures are permeable to proteins of 50-150 kDa, thus Lee does not show obtaining proteins from the media of cultures of protonema (response pg 10).

This is not found persuasive. Lee et al clearly shows that heterologous proteins are found in the medium (column 16, lines 14-45; claim 1). The instant claims are not limited to expressing proteins greater than 150 kDa.

Applicant urges that Lee does not teach or suggest that transformed protonema secrete heterologous protein, and thus does not teach or suggest the steps of the invention (response pg 10).

This is not found persuasive because the rejection is based on a combination of references. Further, *KSR* makes it clear that a teaching, suggestion or motivation does not need to be explicitly provided by the prior art references. Lastly, one of skill in the art would expect protonema, transformed or not, to secrete proteins, as this is a basic cellular function.

Applicant urges that none of the references alone or in combination teach or suggest the claimed invention (response pg 12).

This is not found persuasive. The references in combination do teach the claimed invention.

Applicant urges that Reutter is limited to teaching a method to produce intracellular heterologous protein, and does not teach or suggest how to obtain secreted heterologous protein

from mature protonema; there is no prior art teaching with respect to the secretory production of heterologous proteins in moss (response pg).

This is not found persuasive because Lee provides the teaching of secretory production of heterologous proteins.

Applicant urges that Lee discloses isolation of heterologous protein from a higher plant, which have vascular systems lacking in mosses; the biology of mosses and higher plants is very different, and they have rigid cell wall (response pg 13).

This is not found persuasive because Applicant has provided no evidence that mosses and higher plants have differences in their cell wall structure that would justify thinking that what worked in higher plants would not work in mosses. Differences in vascular systems are not the same thing as differences in cell wall structure. Applicant has not provided evidence that one of skill in the art would think that a protein that could pass through the cell wall of a higher plant could not pass through the cell wall of a lower plant.

Applicant urges that one of skill in the art would not expect the cell walls of protonema to behave the same way as those of tobacco cells in culture, and would not look to higher plant systems for subject matter applicable to lower order plants; thus, there is no legitimate reason to combine Lee with Reutter - Lee is non-analogous art (response pg 13-14).

This is not found persuasive because Applicant has not provided evidence that one of skill in the art would not expect the cell walls of protonema to behave the same way as those of tobacco cells in culture. Reutter teaches that challenges in higher plants are overcome by use of mosses (pg 146, paragraph 2). His comparison does not suggest that art directed to higher plants is non-analogous art for mosses; for example, Reutter used the CaMV 35S and nos promoters

and the nptII selectable marker (pg 144), all which are commonly and first used in higher plant transformation.

Applicant urges that it was known that complete plant organisms fail to secrete the heterologous protein beyond the apoplastic space, citing Lee and Raskin; Lee teaches away from the claimed invention by discussing the disadvantages of using intact plant tissue (response pg 14-15).

This is not found persuasive. Neither Lee nor Raskin teach that in intact plants no proteins ever cross the cell wall. Proteins excreted beyond cell walls could not be collected from a plant grown in the soil - -how would it be done? In a plant grown in the soil, the only way to collect a secreted protein is if it isolated from a contained area, that is, the apoplastic space. As a whole tobacco plant will not grow submerged, collecting the protein from the medium is not an option. The only way to collect a protein expressed in tobacco is isolate from intact plants grown in soil or to grow tobacco cells in a liquid suspension. Raskin also teaches that proteins ARE secreted beyond the cell wall in higher plant cells (column 2, lines 5-7).

Lee does not teach away from the claimed invention. What Lee teaches is that with previous methods, where proteins were intracellularly expressed in intact plants, harvesting the protein required growing the plants (in soil), harvesting them, and extracting the proteins from the plants. An intact tobacco plant, for example, cannot be grown in a liquid suspension culture; however, plant cells can. This allows use of suspension cultures and signal peptides to excrete heterologous proteins into the medium, from which the protein can be isolated. This would be analogous to the way heterologous proteins are produced in bacteria and yeast. There is nothing

in Lee et al that that teaches that intact plants, if they were in a liquid medium, would not secrete proteins in the medium.

Applicant urges that Lee is not capable of suggesting the present invention because of the explicit teaching that intact plants would require extensive extraction procedures to obtain heterologous proteins (response pg 15).

This is not found persuasive because of the way intact higher plants must be grown. An intact tobacco plant cannot be grown in suspension culture.

Applicant urges that secretion through cell walls of intact plants has not been shown in the prior art and Matsumoto indicates that a signal peptide does not guarantee secretion of the heterologous protein through cell walls of tobacco cells; thus, Applicant's claimed invention achieves secretion of heterologous protein into culture medium of whole intact plants, an unexpected result (response pg 15-16).

This is not found persuasive because secretion through cell walls has been shown in the prior art (see Lee et al column 16, lines 14-45; Raskin et al, column 2, lines 5-7). One of skill in the art would not expect that this could not happen in an intact plant were the intact plant submerged in medium. Both Lee and Matsumoto teach that signal peptides can result in secretion of the heterologous protein through cell walls of tobacco cells; the instantly claimed method must only be made obvious over any portion of its scope.

Applicant urges that one of skill in the art would understand that proteins penetrating the cell membrane of an intact plant cell may still be retained by the cell wall, which would serve as a barrier to secretion (response pg 16-17).

This is not found persuasive because Lee, Raskin and Matsumoto teach that signal peptides can result in secretion of the heterologous protein through cell walls (Raskin, column 2, lines 5-7; Lee, column 16, lines 14-45; Matsumoto, pg 1170, left column).

Applicant urges that one of skill in the art would have no reason to expect that the subject matter disclosed by Lee to change the fact that transformed protonema are not expected to secrete heterologous proteins into media; the transformed cells of Reutter are not expect to secrete heterologous protein (response pg 17).

This is not found persuasive because Applicant has provided no evidence that moss protonema were thought to behave differently than higher plants.

Applicant urges that Lee teaches that intact transgenic plants should not expected to secrete heterologous protein; thus one of skill in the art would understand from that the combined disclosures that transformed protonema would not secrete heterologous protein (response pg 17).

This is not found persuasive because at no places does Lee teach that intact transgenic plants should not expected to secrete heterologous protein. What Lee teaches is that cultivation, harvesting and extraction are required if the protein is not secreted. This not the same thing as saying that intact transgenic plants do not secrete heterologous protein, or would not if they could be grown submerged.

Applicant urges that Lee is limited to using single cell suspensions of higher plants to overcome the need to destroy tissue; one of skill in the art would have no reason to expect that by applying Lee's method to intact plants of a lower order that the proteins would be secreted (response pg 17-18).

This is not found persuasive because most plants cannot be grown in liquid suspension culture. Moss protonema can, as demonstrated by Reutter.

Applicant urges that a prima facie case has not been established because there would be no reasonable expectation of success of creating intact protonema that secrete a foreign protein into the media (response pg 18-19).

This is not found persuasive because Applicant has not shown why one of skill in the art would think that moss cells could neo secrete protein or that cells in intact plants behave much differently from plant cells in culture.

Applicant urges that use of a signal peptide does not guarantee that the heterologous protein will pass through the cell wall (response pg 19).

This is not found persuasive because the claims do not require that every signal protein/heterologous protein combination function.

Applicant urges that WO 97/04122 indicates that since 1996 there was a need for a system of intact transgenic plants that could be cultivated without having to use expensive extraction procedures; it and Lee et al acknowledge the inability of intact plants to secrete heterologous protein. The instant invention achieves what was thought impossible (response pg 20).

This is not found persuasive. WO 97/04122 is the national stage application of Lee et al; the specifications and inventors are identical. All responses directed Lee et al apply to WO 97/04122.

Applicant urges that the instant invention achieves success where the prior art does not and meets a long-felt need (response pg 20).

This is not found persuasive because Applicant is misinterpreted Lee. Lee does not indicate that foreign proteins are not secreted from intact transgenic plants into the culture medium. The limitation there is that most plant species will not survive submerged in medium; the limitation is not secretion. One of skill in the art would understand from Reutter et al that protonema overcome that limitation, as protonema survive quite well submerged in medium.

Applicant urges that one of skill in the art would understand from Lee that transgenic plants do not secrete foreign proteins so expensive extraction procedures are needed; Lee teaches that intact transgenic plants do not secrete foreign proteins (response pg 21-22).

This is not found persuasive because Lee does not say that transgenic plants do not secrete foreign proteins.

5. Claims 1-3 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reutter et al in view of Lee et al further in view of Nasu et al (1997, J. Ferm. Bioengin. 84:519-523). The rejection is repeated for the reasons of record as set forth in the Office action mailed 24 September 2007. Applicant's arguments filed 16 May 2008 have been fully considered but they are not persuasive.

The claims are drawn to a method of isolating a heterologous protein from culture medium in which in liverwort protonema were grown.

The teachings of Reutter et al in view of Lee et al are discussed above. Reutter et al in view of Lee et al do not disclose a method of isolating a heterologous protein from culture medium in which in protonema were grown, wherein the protonema were from a liverwort.

Nasu et al teach transformation of *Marchantia polymorpha* (pg 520, left column, paragraphs 1-2). *M. polymorpha* is a photoauxotroph, and thus its growth does not require sugars, vitamins, or phytohormones.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of producing a heterologous protein in protonema tissue as taught by Reutter et al in view of Lee et al, to use liverwort protonema as described in Nasu et al. One of ordinary skill in the art would have been motivated to do so because substitution of one bryophyte for another is an obvious optimization of design parameters. Optimization of parameters is a routine practice that would be obvious for one of ordinary skill in the art to employ to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the use of *M. polymorpha* would have been obvious at the time of Applicant's invention.

Applicant urges that Nasu pertains to cultures of single cells, not to intact plant tissue, and the cells were killed (response pg).

This is not found persuasive because the rejection is based on a combination of references.

Applicant urges that the Gorr declaration of record indicates that Nasu does not teach that heterologous protein produced by transformed Marchantia would be secreted though the cells wall of protonema or a signal peptide; thus, Nasu does not teach or suggest the steps of the invention (response pg 11; 16).

This is not found persuasive because the rejection is based on a combination of references. *KSR* makes it clear that a teaching, suggestion or motivation does not need to be explicitly provided by the prior art references.

Applicant urges that the cells of Nasu are not expected to secrete heterologous protein (response pg 18).

This is not found persuasive because one of ksill ion the art would not expect the cells of Nasu to secrete heterologous protein, as there is not signal peptide linked to them. Reski even indicates that a signal peptide would be required for secretion (Declaration, paragraph 46). Applicant has provided no evidence that if the heterologous protein were linked to a signal peptide and the moss grown as protonema, it would not be expected to be secreted.

Conclusion

6. No claim is allowed.

7. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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Anne Kubelik, Ph.D.
July 12, 2008

/Anne R. Kubelik/
Primary Examiner, Art Unit 1638